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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/042,488	03/16/98	EVANS R	SALK1520-2

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/042,488	Applicant(s) Evans et al
	Examiner Sumesh Kaushal	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-34* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-34* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The instant application is CIP of 08/974,530 filed 10/19/97, now pending which is a CIP of 08/628,830 filed 04/05/96, now pending.

Double Patenting

1. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 25, 26, 29, 31 and 33 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1, 5-13, 16 and 17, of copending Application No. **08,974,530**. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-8, 11-14, 19-20, 22-24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-2, 4, 8-10, 15-26 of copending Application No. **08,628,830**. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15, 17, 27, 28, 30, 32 and 34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 08974530 in view of Mikitani (Biochem. Biophy. Res. Com. 227(2)427-432, 1996). The App.No. 08974530 teaches a pharmaceutical formulation comprising naturally occurring ectysteroid ecdysone and ecdysone analogs but does not teaches an ecdysone mimic. Mikitani teaches the use of non steroidal ecdysone receptor ligand (3,5-di-tert-butyl-4-hydroxy-N-isobutyl-benzamide) which binds to ecdysteroid receptor and regulates the expression of a ecdysone responsive gene. Thus, at the time of filing it would have been obvious to one with ordinary skill in the art to use a nonsteroidal ecdysone mimic to regulate ecdysone inducible expression. One would have been also motivated to use ecdysone mimics in a pharmaceutical formulation because ecdysone mimic are readily available synthetic chemical compounds.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a method for modulating the expression of an exogenous gene in a mammalian subject containing a DNA construct, comprising said exogenous gene under the control of an ecdysone response element and a modified ecdysone receptor which in the presence of a silent partner binds to said ecdysone response element. The method further comprises administering to the subject an effective amount of a non toxic ligand for the ecdysone receptor wherein the ligand is not normally present in the cells. The ecdysone receptor complex receptor have no constitutive activity in mammalian cells and comprises, an ectysteroid ligand binding domain, a DNA binding domain and an transcriptinal activation domain. Claims are also drawn to a pharmaceutically acceptable formulation comprising a at least one ecdysteroid and a pharmaceutically acceptable carrier, wherein the formulation activates ecdysone receptor which in turn modulate the transcription of a gene maintained under the control of an ecdysone response element. Furthermore, claims are also drawn to a pharmaceutically acceptable formulation suitable for oral, topical, nasal, transdermal, intravenous, subcutaneous, interamusclular, intracutaneous, intraperitoneal or intravascular administration. In addition, claims are also drawn to a pharmaceutically acceptable formulation and/or a kit comprising a at least one ecdysteroid and a pharmaceutically acceptable carrier where in said formulation activates ecdysone receptor.

The invention is to a method of modulating the expression of an exogenous gene by creating ecdysone-inducible gene expression in a mammal subject. The ecdysone responsive receptor complex is delivered to the subject via viral and non viral methods, and the expression of a therapeutic gene is induced by the administration of a pharmaceutical formulation carrying an ecydsteroid. (Spec. page 39, line 31-37; page 42, 32-37; page 43, line 1-30; page 26, line 1-9). As claims requires the modulation of expression of a therapeutic gene in a mammalian subject by administering an ecdysone inducible system, the invention lies the realm of gene therapy. The state of the art at the time of filing was such that gene therapy was regarded as an unpredictable art because it had been difficult to predict the transduction efficiency and out come of transduced therapeutic genes (Anderson WF, Nature. 392:25-30, 1998, page 25 col.1, para.1). The art at the time of filing also teaches that various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of appropriate target cells represents the first critical step in gene therapy depending upon the choice and design of a vector used. Although retroviral vectors are the vectors of choice, they require target cells to be in cycling state at the time of infection for the successful delivery of transgenes. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells which results in a transient expression of trangenes without integration of transgenes in host cells. In addition, adenoviral and adeno associated viral vector elicits considerable immunological problems in vivo which affects the sustained expression of transduced genes (Verma et al Nature 389:239-242, 1997, see page 239 col.3 par.2, page 242, table-2). Furthermore, the requirements made of in vivo gene delivery systems are quite demanding, besides limitations in gene transfer the problem to selectively target cells is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter

in vivo and therefor would be diluted out before reaching their targets (Anderson WF Nature. 392:25-30, 1998, page 25 col.2, para.4). In addition, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment (Kay et al, PNAS 94:12744-12746, 1997) Although, gene therapy is a powerful new technology, it is still in the state of development, which renders the state of art unpredictable due to lack of understanding of making recombinant viral particles and their interaction with host cells (Anderson WF, page 30 col.1, para.5). Furthermore, the art at the time of filing also teaches that ecdysone analogs varies in their hormonal potencies which results in the differential regulation of ecydsone induced gene expression. For example, 20-Hydrooxycdysone was found 100 time more active than ecdysone (Nakagawa wt al Steroids 60(5):401-405, 1995; page 402. col.2, para.2 lin.1).

The specification teaches ecdysone responsiveness in a cell line (N13) containing the modified ecdysone receptor VpEcR, a hetrodimeric partner (RXR) and an ecdysone inducible reporter gene (page 51, example-3). The cell line exhibited dose response to muristerone treatment by expressing reporter genes (page 52, line 4-14). The specification also teaches the bioavailability and toxicity of muristerone in a mice_ by injecting mice with 10mg of muristerone interaperitoneally. The blood sample were then analyzed for muristerone activity by incubating serum on transfected CV-1 cells (page 52, example-4). Furthermore, the specification articulates the muristerone dependent gene expression in transgenic mice encoding VgEcR, RXR and DNA activation domain (page 53, example-5). The specification teaches the preferred gene transfer vector is retroviral vector for the delivery of ecdysone inducible gene expression (page 42, line 22-23). However, the specification fails to demonstrate the activation of a any and all therapeutic genes in a mammalian

subject by administering a naturally occurring ecdysone, an ecdysone analog or an ecdysone mimic. The specification fails teach the delivery of ecdysone inducible system containing a therapeutic to a mammalian subject using a retroviral vector. The specification does not provide any guidance to routes of delivery, dosage amount, dosage frequencies and target cells for any vector to create ecdysone inducible responsiveness in a mammal, which results in the induction of a therapeutic gene in response to an ecdysteroid pharmaceutical formulation. Moreover, the pharmaceutically acceptable formulation (and/or a kit) comprising a at least one ecdysteroid and a pharmaceutically acceptable carrier is not enabled because specification fails to provide guidance that such a pharmaceutical formulation results in induction of a therapeutic gene a mammalian subject. The word " Pharmaceutical" means the administration of a medicinal drug of therapeutic value, which have a characteristic interaction in a body, in terms of its absorption, distribution, metabolism and excretion (see Pharmaceutical and related terms in Merriam Webster's Dictionary). The instant specification also fails to provide a therapeutic effect of any ecdysteroid pharmaceutical formulation in any and all mammals because it only provided guidance for monitoring β-galactosidase or Luciferase activity in N13 cell line in response to different concentrations of Muristerone-A. The Pharmaceutical effect of such formulation could not be justified because applicant speculates the efficacy of therapeutic genes in view of β-galactosidase or Luciferase expression in a N13 cell line. Furthermore, considering the state of the art a the time of filing invitro transfection of a cell line with plasmid DNA does not represent the in-vivo transfer of ecdysone inducible system in a mammal. Moreover, the applicant fails to provide any guidelines for determining which individual need to be administered with said pharmaceutical formulation because an ecdysone inducible therapeutic gene should be in place in the host before the administration of such formulation. Furthermore, the specification fails to show that a pharmaceutical formulation carrying any ecdysteriod or its analogs

or mimics (as claimed) is equally effective in the modulation of a gene in a mammalian subject because various ecdysteriod are know to induce different level of induction in an ecdysone responsive system. Thus, without guidance not provided in the specification and considering the state of art, the skilled artisan at the time of filing would be lacking a reasonable expectation of success to a method of modulating the expression of an exogenous gene in a mammalian subject, the method for expressing a recombinant product detrimental to a host and the pharmaceutical formulation carrying an ecydsteroid, without an undue amount of experimentation.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-29, 31-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Meybeck et al (US Pat. No. 5198225, 3/30/93). Maybeck et al teaches a pharmaceutical composition comprising at least one ecdysteriod or ecdysteroid derivatives in admixture with pharmaceutically acceptable excipient (see col.9, lin.57). Thus Meybeck et al clearly anticipate the claimed pharmaceutically acceptable formulation.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meybeck et al (US Pat. No. 5198225, 3/30/93) and further in view of Mikitani (Biochem. Biophy. Res. Com. 227(2)427-432, 1996). Maybeck et al teaches a pharmaceutical composition comprising at least one ecdysteriod or its derivatives in admixture with pharmaceutically acceptable excipient (see col.9, lin. 57). However, Maybeck et al does not teach the use of such pharmaceutical composition comprising of a ecdysone mimic. Mikitani teaches the use of non steroidal ecdysone receptor ligand (3,5-di-tert-butyl-4-hydroxy-N-isobutyl-benzamide) binds to ecdysteroid receptor and regulates the expression of a ecdysone responsive gene. Thus, Mayback teaching the pharmaceutically acceptable formulation comprising an ecdysone hormone and Mikitani teaching the use of a ecdysone mimic, it would have been obvious to one with ordinary skilled in the art to make a pharmaceutically acceptable formulation comprising ecdysone, ecdysone analogs or a ecdysone mimic. One would have been also motivated to use ecdysone mimics in a pharmaceutical formulation because ecdysone mimic are readily available synthetic chemical compounds.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM . If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brian Stanton Ph.D. can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

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